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EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/781,010	KOIZUMI ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,22 and 24-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,22 and 24-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/18/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The Application is a continuation of the US application No. 09/068,525. Supplemental Preliminary Amendment of Sep. 21, 2004 is acknowledged. The amendments to the claims and specification have been entered as requested. Claims 1-20 of the parental application have been canceled and claims 21-33 have been entered in preliminary amendment filed with the application. Claim 23 has been recently canceled; claims 21-23, 24-25 29-31 and claim 33 have been amended. Claims 21-22 and 24-33 are pending in the application and are the subject of this Office Action.

DETAILED ACTION

1. *Objections*

1.2. Specification

The objection for a vague description of the term "complex carbohydrate" on page 17 is withdrawn, because the specification has been amended.

The objection of the specification for lack of the term "product of a culture", which was used by claims is withdrawn, because the amended claims do not recite the term.

2. Rejections

2.1. 35 USC section 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 21, 22, 24-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21, 22, 24-33 are confusing in recitation of the term "treated product of [emphasis added] said yeast cells" and further for the description:

"wherein said treated product is

a dried product of the cells,

a freeze-dried product of the cells,

a surfactant product of the cells,

an ultrasonic-treated product of the cells,

a mechanically disrupted product of the cells,

mechanically disrupted product of cells,

solvent treated product of the cells,

enzyme-treated product of the cells,

a protein fraction of the cells,

an immobilized product of the cells, or

an enzyme preparation obtained by extraction from the cells."

To use the invention as claimed, the product of the cell has to contain the necessary enzyme(s), i.e. it has to contain all proteins produced by cell, thus including the enzyme necessary for performing the method of synthesis of a complex carbohydrate. It is unknown what

surfactant product of cell,

solvent treated product of the cells,

enzyme-treated product of the cells,

a protein fraction of the cells,

an immobilized product of the cells, or

an enzyme preparation obtained by extraction from the cell

still contain the necessary enzymes absent a detail teaching of particular method of cell treatment. Thus, it is not clear which products of cell listed above are excluded or included in the scope of the claims.

Traversing the rejection Applicants write, "It is noted the language objected to is 'treated products of' cells, not 'treated products obtained from' cells. Therefore, respectfully submitted, the Examiner's position in which the 'dried product of the cell' includes separated components constituting the cell is unreasonable", page 9, the end of the second paragraph.

Applicants' argument has been fully considered, but is found not persuasive for the following reasons. In the art the term "a product of cell" is used to mean "a product obtained from cell", i.e. an isolated product, as well as a product produced by cell wherein said product does not need to be isolated in any way. As long as the application is silent about details of treating cells to obtain the product, for example, which surfactants, under which temperature, time of treatment, buffer and pH are used, one skilled in the art does not know whether the product contains the necessary enzyme.

2.2. 35 USC, section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3.2.1. Biologic deposit

Claims 30 and 33 are rejected for lack of biologic deposit for the same reasons for which parental claims 17 and 20 were rejected. The reasons are stated in the prosecution of the parental case 09/068,525, Office Actions of August 18, '03 and November 12, '02.

Claim 20 was rejected under 35 U.S.C. § 112, first paragraph, because the specification was lacking the description of biologic deposit. The invention appeared to employ a novel plasmid and transformant of namalwa cells called namalwa KJM-1/pAMoERSAW1containing said plasmid. Since the plasmid/transformant were essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The sequence of claimed plasmid was not disclosed, nor had all the sequences required for their construction were shown to be publicly known and freely available. The enablement requirement of 35 U.S.C. § 112 might be satisfied by deposit of the plasmid/transformed

namalwa cells. The specification did not disclose a repeatable process to obtain the transformed cell. Accordingly, it was deemed that a deposit of the transformed cell should had been made in accordance with 37 C.F.R. § 1.801-1.809.

In the previous Response (amendment May 15, '03) to the above rejection, Applicants stated, the namalwa KJM 1/pAMoERSW1 cell line could be easily obtained, without undue experimentation, according to the method described by Example 2 of the Japanese Published Unexamined Patent Application No.181759/94 as discussed in Example 4 of the parent specification. The sworn translation of Example 2 of the Published Application was enclosed to the previous Response. This argument of Applicants was found not persuasive for the following reasons:

1. Example 2 of the Japanese Published Unexamined Patent Application No. 181759/94 (JP59/94) did not mention what is the source of KLM-1 namalwa cells and whether the cells were publicly available.

2. The Example 2 of the (JP59/94) did not enable one skilled in the art to make the namalwa KJM-1/pAMoERSW1 transformant, because the plasmid pAMoERSW1 was not enabled. Construction of said plasmid was preceded by stepwise constructing four new plasmids, which involved five previously known plasmids for which the source is not stated. For example, the source of plasmid pASN6 is unknown; the source of pAGE207 and pAMERC3Sc was given as Example 1, 1(11) (13) of presumably JP59/94 which is untranslated; the source of plasmids pAGE107 and pPMOLI was given as JP-A-22979

and JP-A-1 63394, but the translations of these documents was not provided by Applicants.

3. Example 4 of the parental application was directed to the method of isolating of β1, 3-galactosyltranferase from the medium in which the namalwa KJM-1/pAMoERSW1 cells were cultivated and not to the process of transformation of namalwa KJM-1 with the pAMoERSW1 plasmid.

Claim 17 was rejected for lack of biologic deposit of the recombinant namalwa KJM-1 cell that are necessary to make and use the claimed invention. Applicants' argument that the recombinant namalwa KJM-1/pAMoERSW1 cells can be easily obtained without undue experimentation is found not persuasive as addressed above under 1 and 2.

In their current Remarks, on page 8, Applicants' position regarding the above rejection is that 1) plasmid AMoERASW1 is "routinely" prepared from eight plasmids that are not proprietary, but described in the quoted prior art, including 7 articles in scientific journals and American and Japanese patent, and that 2) namalwa KJM-1 cells as such are easily be prepared according to Cytotechnology 1990, 3, 133. Furthermore Applicants believe the articles and patents quoted on page 8 of their Response are of record.

The Applicants arguments are found not persuasive for the following reasons.

The quoted prior art is not of record, with exception of the Japanese patent 181759/94. The articles and the US patent are not referenced to in the specification. Thus, one skilled in the art is not guided as to the source of the plasmids and their public availability. Even if articles were referenced to in the specification, providing the description of steps in obtaining the eight plasmids used in engineering the ninth one, plasmid pAMoERSW1, is not enabled absent teaching of particular fragments and restriction enzymes used in the construction of pAMoERSW1. Plasmid pAMoERSW1 is not prepared routinely; these are the inventors who prepared it. Since preparation of the plasmids from the quoted articles is not always simple, one of skills in the art realizes that preparation of pAMoRSW1 is complex. For example, preparation of plasmid pKCR according to Proc. Natl. Acad. Sci. USA, 78, 1527 (1981), according to the authors, "is rather convoluted"; see page 1528, left column, second paragraph of RESULTS (copy enclosed).

Regarding point 2), namalwa KJM-1 taught by Cytotechnology 1990, 3, 133, are "human lymphoblastoid cell line obtained from Mr. F. Klein (Frederick Cancer Research Center, Frederic, Maryland, USA)"; see page 134, Materials and Methods, first line. Thus, these cells are not publicly available.

In summary, plasmid pAMoERSW1, namalwa KJM-1 as such, and namalwa KJM-1/pAMoERSW1 are not publicly available, therefore the claims are rejected.

2.2.1. Lack of written description

Claims 21, 22, and 24-33 are rejected in the previous Office Action, paper No. 28, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 21, 22, and 24-33 are rejected for reasons stated in rejection of claims 2, 3, 7-12, 16-20 of the parental case, Office Action of August 18, '03, and November 12, '02 .

Claim 21, 22, 24-33 are directed to a process for producing uridine diphosphate sugar and a complex carbohydrate, which comprises:

1) selecting as a first enzyme source, a yeast cell, selected from the group consisting of Sacharomyces and Kluyveromyces, or treated product thereof, said yeast cells or treated product being capable of producing a uridine diphosphate sugar form a nucleotide precursor selected from the group consisting of orotic acid, uracil, orotidine and uridine, an a sugar;

2) carrying out an enzyme reaction in a first aqueous medium containing the first enzyme source, the nucleotide precursor and the sugar to form and accumulate the uridine diphosphate sugar in the first aqueous medium;

3) recovering the uridine diphosphate sugar from a supernatant of the first aqueous medium;

4) selecting as a second enzyme source a microorganism or animal cell, or a treated product thereof, capable of producing a complex carbohydrate from the uridine sugar and a precursor of complex carbohydrate:

5) carrying out and enzyme reaction in a second aqueous medium containing the second enzyme source, the precursor of complex carbohydrate and the uridine diphosphate sugar to form and accumulate the complex carbohydrate in the second medium, and

6) recovering the complex carbohydrate from the first or second aqueous medium.

The amended claim Claims 21 and 22 are directed to the process for producing sugar nucleotide and complex carboxydrate when the "treated product of cells" is used. The treated product of cells used in the process is any species of a genus comprising the following genera:

1) dried product of cells

2) freeze -dried product of the cells,

3) surfactant-treated product of cells,

3) ultrasonic and mechanically disrupted product of the cells,

4) mechanically disrupted product of cells,

4) solvent treated product of the cells,

5) enzyme-treated product of the cells,

6) a protein fraction of the cells,

7) an immobilized product of the cells, or

8) an enzyme preparation obtained by extraction from the cells,

wherein the species of genera 1) - 8) are capable of producing a uridine diphosphate sugar form a nucleotide precursor selected from the group consisting of orotic acid, uracil, orotidine and uridine and sugar or/and are capable of producing a complex carbohydrate from the uridine sugar and a precursor of complex carbohydrate.

The claims are reciting a large genus and subgenera of treated cell products. The disclosure is silent as to what genera of 1)-8) should be. Applicants only list the above enumerated genera of products on page 16, but Applicant fail to describe the above products in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To clarify the subject the examiner is turning the Applicants' attention to the following.

1. "The treated product of cell" is a generic term the scope of which covers thousands of variable products obtained by enormous number of methods. This genus has many subgenera, some of which are listed above under 1)-8). Applicants do not teach which "treated product of cell' is the source of enzymes necessary for production of sugar nucleotide or/and complex carboxydrate.

2. Particular subgenus, for example 1), encompasses any product of cells that is dried by any method. The product may be dried cell membrane, dried

components of cytosol, dried nuclei, dried whole cells, dried mitochondria, dried whole cell proteins extracted by any method, dried crude extracts of any enzymes, dried purified enzymes. The drying method can be freeze and dry, dried from alcohol solution or other organic solution, dried at room temperature, dried at elevated temperature, dried by centrifugation in the vacuum.

3. Some methods of drying of cell product are not suitable for preserving the enzymatic activity of the enzymes of interest. For example, drying at high temperature may destroy the enzymatic activity.

Applicants teach only two representative species of the large and variable genus of treated products of cells, i.e., dried backer's yeast and β1, 3-galactosyltranferase from a namalwa line KJM-1 transformed with a plasmid pSMoERSAW1. This is, however, not sufficient to provide the identifying characteristic of all other species of the genus, as claimed. Thus, because Applicants did not provide identifying characteristics of the genus of treated products of cells, as claimed, one skilled in the art is not convinced that Applicant were in possession of the claimed invention when the application was filed.

Claim 30-33 are rejected as directed to a method of producing complex carbohydrate, wherein the method COS7 and namalwa KJM-1 cells transformed with a plasmid comprising DNA encoding β1, 3-galactosyltranferase or β1, 3-

galactosyltranferase from human melanoma WM266-4, or the namalwa KJM-1/ pAMoERSW1 cell. The claims are directed to a large genus of COS-7 and namalwa KJM-1 cells transformed with β1, 3-galactosyltranferase genes, from all possible natural and man-made sources, for which the description of structure is lacking in the disclosure. Applicants even do not present the structure of a single representative species of the genus, i.e., plasmid pAMoERSW1 comprising DNA encoding β1, 3-galactosyltranferase from human melanoma WM266-4 cells that was used to transform COS7 and namalwa KJM-1 cells.

Therefore, one skilled in the art is not convinced that Applicants were in possession of the claimed invention when the application was filed.

3.2.2. Scope of enablement

Claims 21, 22, 24-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for production of uridine diphosphate sugar by the treated product of *S. cerevisiae* cell that is dried *S. cervisiae*, and production of complex carbohydrate by the treated product of animal cells which is commercially available β1,3-galactosyltranferase does not reasonably provide enablement for production of uridine diphosphate sugar and complex carbohydrates by:

1) any dried product of cells,

2) any freeze-dried product of the cells,

3) any surfactant-treated product of cells,

3) any ultrasonic and mechanically disrupted product of the cells,

4) any solvent treated product of the cells,

5) any enzyme-treated product of the cells,

6) any protein fraction of the cells,

7) any immobilized product of the cells, or

8) any enzyme preparation obtained by extraction from the cells,

wherein the species of genera 1) - 8) are capable of producing a uridine diphosphate sugar form a nucleotide precursor selected from the group consisting of orotic acid, uracil, orotidine and uridine and sugar or/ and are capable of producing a complex carbohydrate from the uridine sugar and a precursor of complex carbohydrate.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The scope of the claims encompasses large genus of treated cell products. As stated above in rejection for lack of written description, the specification is silent as to what particular species of the subgenera 1)-8 are suitable to make the invention.

In addition, the specification does not teach how to use

1) any dried product of cells

2) any freeze -dried product of the cells,

3) any surfactant-treated product of cells,

3) any ultrasonic and mechanically disrupted product of the cells,

4) any mechanically disrupted product of cells,

4) any solvent treated product of the cells,

5) any enzyme-treated product of the cells,

6) any protein fraction of the cells,

7) any immobilized product of the cells, or

8) any enzyme preparation obtained by extraction from the cells

in production of uridine diphosphate sugar and complex carbohydrates as claimed in he claims.

The scope of the claims is not in accordance with the scope of enablement. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses production of uridine diphosphate and complex carbohydrates by

1) any dried product of cells,

2) any freeze -dried product of the cells,

3) any surfactant-treated product of cells,

3) any ultrasonic and mechanically disrupted product of the cells,

4) any mechanically disrupted product of cells,

4) any solvent treated product of the cells,

5) any enzyme-treated product of the cells,

6) any protein fraction of the cells,

7) any immobilized product of the cells, or

8) any enzyme preparation obtained by extraction from the cells,

wherein the species of genera 1) - 8) are capable of producing a uridine diphosphate sugar form a nucleotide precursor selected from the group consisting of orotic acid, uracil, orotidine and uridine and sugar or/ and are capable of producing a complex carbohydrate from the uridine sugar and a precursor of complex carbohydrate.

The specification provides some enablement for production of uridine diphosphate sugar, which is limited to dry yeast cells (one species, *S. cerevisiae*) suspended in a buffer containing glucose. The specification is lacking examples and instruction as to the performance of synthesis of uridine diphosphate by other treated products of yeast cells listed under 1)-8) above.

Enablement for production of complex carbohydrates by the treated products of cells is limited to the treated product that is commercially available, namely, β1, 3-galactosyltranferase.

One skilled in the art concludes that Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claim. The probability of success in making the invention in result of extensive experimentation is extremely low.

Thus, the experimentation left to those skilled in the art is improperly extensive and undue.

2.3. 35 USC section 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21, 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caputto et al. (Isolation of the Coenzyme of the Galactose Phosphate-glucose Phosphate Transformation, J. Biol. Chem. 1950, 184, 333-350, a copy of the article was attached to the rejection in the prosecution of the parental case) in view of the common knowledge in the art.

Claim 21 is directed to production of uridine diphosphate sugar using Sacharomyces yeast cells cultivated in medium comprising substrates for uridine, i.e. orotic acid, uracil, orotidine and uridine itself as well as a sugar.

Caputto et al. were the first to teach the compound which is uridine diphosphate sugar, namely uridine diphosphate glucose. They use as the source of this compound baker's yeasts: see page 343, line 17 and page 349 line 25.

Caputto et al. do not disclose the conditions of cultivation under which the 5 kilos of baker's yeast used for isolation of the uridine diphosphate glucose were grown before extraction of the compound. However, it would have been obvious to one having ordinary skill in the art at the time of invention to have baker's yeast as Caputto et al. did and cultivate them in the medium comprising precursors of uridine diphosphate glucose, i.e. orotic acid, uracil, orotidine and uridine itself, as well as a glucose (Example I), for efficient production of the compound by fermentation of microorganism routinely used in biotechnology. The motivation would be to provide a method of cheap production of uridine diphosphate sugar on industrial scale. The expectation of success is 100%, because Caputto et al. have shown that the baker yeast produce the compound, and the technology of yeast fermentation is very well known in the art. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Traversing this rejection Applicants write, "Capputto does not suggest the yeast cell incorporates the substrate nucleotide precursor from outside the cell and produce UDP-glucose extracellularly using glucose as another substrate" page 11 of the remarks, the end of the first paragraph.

This Applicants' argument is found not persuasive for the following reasons.

1) Yeast cell transport (incorporates) from the culture medium chemical components for synthesis of chemicals necessary for cell metabolism.

Yeast cell may use, for example, uracil ready in the medium for further synthesis of uracil phosphate glucose or can itself synthesize uracil and further use it for synthesis of uracil phosphate glucose. Uridine is uracil triphosphate, which is a precursor of uracil diphosphate glucose. Uridine may be transported to yeast cell and used for further synthesis of uracil diphosphate sugar, or may be synthesized inside the yeast cell and than used for further synthesis of the uracil diphosphate sugar. These facts are basic facts in biochemistry known to one skilled in the art, therefore they do not need to be taught by a prior art because they are taught in biochemistry courses.

2) Applicants attention is turn to the fact that the rejected claims are not directed to production of UDP-glucose extracellularly, but by enzyme sources (yeast cells or their lysates) in an aqueous solution. Thus, Applicants' argument that the prior art does not teach the extracellular production of UDP is moot.

In conclusion, claims 21, 24 and 25 are rejected 35 U.S.C. 103(a) as obvious over Caputto's disclosure.

Claims 21, 24, and 25 are also rejected under 35 U.S.C. 103(a) as being unpatentable over review by Herscovics et al. Glycoprotein biosynthesis in yeast,

FASEB J. 1993, 7, 540-550), in view of common knowledge in use of S. cerevisiae in biotechnological processes.

The claim is directed to production of uridine diphosphate sugar using Sacharomyces yeast cells cultivated in medium comprising substrates for uridine, i.e. orotic acid, uracil, orotidine and uridine itself as well as a sugar.

Herscovics et al. teach that S. cerevisiae synthesize sugar donors, page 541, left column, section "Synthesis of Sugar Donors", particulary UDP-GlcNac. It would have been, therefore, obvious for the skilled artisan to use the culture of S. cerevisiae for production of UDP- GlcNac. Herscovics et al. do not disclose the conditions of cultivation of S. cerevisiae wherein said conditions are particularly suitable for production of UDP-GlcNac.

However, it would have been obvious to one having ordinary skill in the art at the time of invention to have S. cerevisiae as Herscovics et al. teach, and cultivate them in the medium comprising precursors of uridine diphosphate glucosoamine, i.e. orotic acid, uracil, orotidine and uridine itself, as well as a glucosamine (Example III), for efficient production of the compound by fermentation of microorganism routinely used in biotechnology. The motivation would be to provide a method of cheap production of this uridine diphosphate sugar on industrial scale. The expectation of success is 100%, because of the teachings of the review article, the technology of yeast fermentation is very well known in the art. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Traversing this rejection Applicants state, "Herscovic does not suggest that yeast incorporates a nucleotide precursor from outside of the cell and has activity of extracellularly producing UDP-GlcNAc using maltose and glucosamine as substrates", page 11, third paragraph.

This Applicants' argument is found not persuasive for the following reasons.

Yeast cell transport nucleotide precursor from the culture medium i.e. form outside of the cell. Yeast cell transports uracil, a nucleotide precursor, from the medium for further synthesis of uracil diphosphate sugar. The fact is a basic fact in biochemistry, and not Inventior's finding, and, as such, does not need to be taught by a prior art, because it is taught in biochemistry courses. In addition, Applicants attention is turn to the fact that the rejected claims are not directed to production of of UDP-GlcNac extracellularly, but by enzyme sources (yeast cells or their lysates) in an aqueous solution. Thus, Applicants' argument that the prior art does not teach the extracellular production of UDP is moot.

In conclusion, claims 21, 24 and 25 are rejected 35 U.S.C. 103(a) as obvious over Herscovic's disclosure.

Claim 22, 24, 25, 27, 29 rejected under 35 U.S.C. 103(a) as being unpatentable over Tochikura et al. (Sugar Nucleotide Fermentation by Yeast, Ferment. Technol. Today, 1972, 463-471; Proc. IVth Int. Ferment. Symp., copy enclosed), further in view of Ichikawa et al. Expression cloning of a cDNA for human ceramide glucosyl transferase

that catalyzes the first glycosylation step of glycosphingolipid synthesis, Proc. Natl. Acad. Sci. USA, 1996 (May) pp. 4638-4643 and in view of the common knowledge in the art.

Claim 22 is directed to a process for producing a complex carbohydrate, which comprises:

1) selecting as a first enzyme source, a *Sacharomyces* cell being capable of producing a uridine diphosphate sugar form a nucleotide precursor selected from the group consisting of orotic acid, uracil, orotidine and uridine, an a sugar;

2) carrying out an enzyme reaction in a first aqueous medium containing the first enzyme source, the nucleotide precursor, and the sugar to form and accumulate the uridine diphosphate sugar in the first aqueous medium;

3) recovering the uridine diphosphate sugar from a supernatant of the first aqueous medium;

4) selecting as a second enzyme source a microbial cell, or a treated product thereof, capable of producing a complex carbohydrate from the uridine sugar and a precursor of complex carbohydrate:

5) carrying out and enzyme reaction aqueous medium containing the second enzyme source, the precursor of complex carbohydrate and the uridine diphosphate sugar to form and accumulate the complex carbohydrate in the first or second medium, and

6) recovering the complex carbohydrate from the first or second aqueous medium.

Tochikura et al. teach S. cerevisiae fermentation as an efficient way for production UDPglucose; page 463, the section "*Reaction Conditions for the Fermentation*". Tochikura et al. also teach that the UDP sugars are important in the synthesis of carbohydrates; see "Introduction", page 463. However, Tochikura et al. do not teach how to use the UDPglucose for synthesis of complex carbohydrates by a microbial organism/transformed microbial organism.

Ichikawa et al. teaches an E. coli cells expressing ceramide glucosyl transferase ß1-1' from human melanoma cell line SK-Mel-28. This enzyme uses as precursor UDPglucose and transfers it to ceramide (UDP-glucose:ceramide ß1-1'glucosyltransferase); see section "**Expression of GlcT-1 in E. coli**" page 4639, right column. Glucose ceramide (GlcCer) serves as a core structure for more than 300 of complex carbohydrates that are called glycosphingolipids; see the definition on page 17 of the instant application.

Ichikawa also teaches a treated product of the microbial cells, because he teaches the cells disrupted by sonication (page 4639, right column line 20). Thus, Ichikawa teaches a microbial cell and treated product thereof that synthesize complex carbohydrates.

It would have been obvious to one having ordinary skill in the art at the time of invention to combine the Tochikura et al. and Ichikawa et al.'s teachings, and have the S. cerevisiae culture as the source of UDP-glucose and the E. coli transformed with

human ceramide ß1-1'glucosyltransferase as a source of the enzyme necessary for synthesis of complex carbohydrates. Because the transformed E. coli expresses the enzyme with high efficiency the UDP-glucose substrate should be available in high quantities, therefore it should be added to the medium in which the E. coli transformant is cultivated.

The motivation would be provided by the common knowledge in the fermentative production of compound of interest, wherein the skilled artisan seeks efficient microorganism source of substrate and enzyme for producing the compound on industrial scale. The expectation of success is 100%, because Tochikura et al. have shown that S. cerevisiae can be used in efficient fermentative production of UDP-glucose, and Ichikawa et al. has shown that the E. coli produces the enzyme necessary for production of complex carbohydrate from uridine phosphate sugar. Thus, combining both teachings to make the claimed invention was within the ordinary skill in the art at the time the invention was made and was as a whole, *prima facie* obvious.

Traversing this rejection Applicants state, "Tochikura shows that ground yeast synthesize UDP-sugar from UMP. However, Tochikura does not suggest that orotic acid, orotidine, uridine, and uracil(including UMP) are incorporated into a yeast cell through cell membrane" page 11, the forth paragraph.

This Applicants' argument is found not persuasive for the following reasons.

Yeast cell transports nucleotide precursor from the culture medium i.e. form

outside of the cell. Yeast cell transports enumerated small molecules, which are nucleotide precursors, from the medium for further synthesis of uracil diphosphate sugar. This fact does not need to be taught by a prior art, because it is taught in biochemistry courses.

In conclusion, claims 21, 24 and 25 are rejected 35 U.S.C. 103(a) as obvious over Herscovic's disclosure.

3. Conclusion

All claims are rejected.

This is a continuation of applicant's earlier Application No. 09/068,529. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m. If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-1600. The fax phone number for this Group is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 872-9306.

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